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(54) Instant oral-release capsule containing nifedipine.

(57) The invention concerns an instant oral-release capsule containing an aqueous or aqueous alcoholic solution of nifedipine, containing a polyalkylene glycol and a polyoxyethylene ester component, the amount of the ester component in the solution being sufficient to prevent precipitation of nifedipine in the mouth of a patient after release of the solution from the capsule. Preferably, the ester component is an ethoxylated hydrogenated castor oil Cremophor RH40. The solution may further contain a second glycol component, especially glycerol.

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Instant oral-release capsule containing nifedipine

The invention concerns an instant oral-release capsule containing nifedipine in solution.

Pharmaceutical nifedipine preparations in the form of soft gelatin oral-release capsules are of major importance in the treatment of coronary deceases. When needed, a capsule is bitten by the patient, so that the solution is released from the capsule into the patient's mouth. Immediate action of the nifedipine is desired, so that the absorption of the capsule's nifedipine content by body tissues must be as fast as possible; on the other hand, the nifedipine must remain in the patient's body for the required duration.

The absorption of solid nifedipine by body tissue proceeds very slowly, so that solid nifedipine preparations are unsuitable for coronary therapeutical applications. The absorption of nifedipine from solutions is much faster.

Nifedipine dissolves in aqueous media only to a very small extent, so that aqueous solutions cannot provide the nifedipine concentrations required for therapeutical purposes. Nifedipine dissolves much better in polyalkylene glycols, especially upon moderate warming. In prior art, therefore polyalkylene glycol solutions of nifedipine have been used in an attempt to achieve the required bioavailability of nifedipine.

Such prior art capsules are known from DE 22 09 526. This patent discloses an oral-release capsule with a soft gelatin capsule body containing a solution of nifedipine in, substantially, a mixture of polyethylene glycol and glycerol. Such capsules have for years been marketed under the name "Adalat" ™.

Yet these known capsules do not achieve instantaneous maximal bioavailability of nifedipine. One reason for this disadvantage appears to be the fact that nifedipine solubility decreases once the capsule solution is released from the capsule and mixed with aqueous body fluids, especially saliva. Part of the nifedipine is then precipitated from the solution, so that the absorption is slowed down, resulting in a delay in reaching the required nifedipine blood level.

For alternative nifedipine formulations, i. e. sublingual sprays, an attempt at overcoming related problems was described in EP 240 484. According to this prior art, a nifedipine spray solution should contain a combination of polyvinylpyrrolidone, copolyvidone, propylene carbonate and an emulsifier. The compositions disclosed in this prior art are not suitable for capsules. For several reasons, especially in view of the problems involved in administering exact nifedipine dosage amounts through spraying, nifedipine sprays are less advantageous than capsules.

It is therefore an object of the invention to provide an instant oral-release capsule capable of providing instantaneous maximal bioavailability of nifedipine.

It is a further object of the invention to provide such a capsule, achieving at the same time substantially the same duration of nifedipine bioavailability in the patient's body as provided by prior art capsules.

These and other technical objects and advantages are achieved by an instant oral-release capsule containing an aqueous or aqueous alcoholic solution of nifedipine, a polyalkylene glycol and a polyoxyethylene ester component, the amount of the polyoxyethylene ester component in the solution being sufficient to prevent precipitation of nifedipine in the mouth of a patient after release of the solution from the capsule.

The invention advantageously prevents nifedipine precipitation in the mouth of the patient, after the solution is released from the capsule and mixed with aqueous media such as saliva, gastro-intestinal fluids etc. This is probably largely due to the presence of the polyoxyethylene ester component in the solution, although it is assumed that synergistic effects are present, the polyalkylene glycol and water in the solution assisting the precipitation-preventing action of the polyoxyethylene ester component.

The polyoxyethylene ester has hydrophilic and lipophilic groups, which are probably responsible for the precipitation-preventing effect. The ester component can thus be regarded as an emulsifier.

A variety of polyoxyethylene ester components are usable in the context of the invention, but of course they must be non-toxic and pharmaceutically acceptable. Preferably, the ester component should also be neutral in taste. Polyoxyethylene ester components usable in the context of the invention comprise ethoxylated glycerides, especially mono- or triglycerides; ethoxylated fatty acid esters; ethoxylated castor oil derivatives and mixtures of two or more of such substances.

It is especially advantageous to use ethoxylated hydrogenated castor oil products as the polyoxyethylene ester component; an especially preferred such product is commercially available under the name Cremophor RH40.

The amount of the polyoxyethylene ester component in the solution should be between about 3 and 33 weight percent and preferably about 7 to 15 weight percent of the solution. Chosing the most suitable concentration of the polyoxyethylene ester component in the solution is substantially a matter of com-

promise; higher contents of the ester component allow higher degrees of dilution with aqueous media, before precipitation of nifedipine sets in, but on the other hand such higher ester component contents increase the danger of the solution's taste being adversely affected. At the above-mentioned concentrations, taste is practically unimpaired, while no precipitation of nifedipine is observed under usual conditions, neither in the mouth nor in the gastro-intestinal tract.

The polyalkylene glycol component of the solution is preferably a polyethylene glycol (PEG). The PEG should have an average molecular weight smaller than 2000; presently, the PEG is most preferred to have an average molecular weight of about 400. The amount of the PEG or other polyalkylene glycol in the solution is preferably between about 50 and 90 weight percent. Presently most preferred is a PEG concentration in solution of about 70 to 85 weight percent.

While it is thus possible to use a solution containing (besides water, taste-improving substance if required and, of course, nifedipine) only PEG 400 and Cremophor RH_{40}, especially in a 9 to 1 weight percent ratio, it is presently more preferred to further add a second glycol component to the solution, especially if this second glycol component is glycerol. The amount of this second glycol component, especially glycerol, in the solution can advantageously lie between about 2 and 15 weight percent, and most preferred at about 5 to 10 weight percent.

An instant oral-release capsule forming what is presently regarded as the best embodiment of this invention contains about 500 mg of solution, the solution containing about 10 mg nifedipine, about 403 mg polyethylene glycol with an average molecular weight of about 400, about 35 mg glycerol, about 41 mg ethoxylated hydrogenated castor oil Cremophor RH40 and about 9.5 mg water, about 1.5 mg peppermint oil and artificial sweetener being added as taste-improving substances. The capsule body is formed of soft gelatin and contains light-protective pigments, since nifedipine is highly light-sensitive. The capsule body of this embodiment weighs about 200 mg, so that the overall weight of the oral-release capsule is about 700 mg.

The invention will now be described in greater detail, comparing the effects achievable through the invention with those of the prior art capsules, similar to those disclosed in DE 22 09 526.

For the comparative tests to be described in detail hereinafter, instant oral-release capsules (A) according to the invention were prepared, which only slightly differ from the above-mentioned presently most preferred embodiment of the invention.

These capsules had a capsule body consisting of gelatin with a content of glycerol as a softening agent. The capsule body further contained light-protective pigments, namely titanium(IV)oxide, yellow iron oxide, red iron oxide and brown iron oxide. The capsule body further contained minor amounts of sodium benzoate salts. The overall weight of the capsule body was approximately 200 mg.

These capsule bodies were each filled with approximately 500 mg of solution. The solution contained 10 mg nifedipine, dissolved in a mixture of about 35 mg glycerol, about 370 mg PEG 400, about 41 mg Cremophor RH40, about 44 mg water and, as taste-improving substances about 1.5 mg peppermint oil and sweetener (saccharin sodium).

The overall weight of the oral-release capsule was thus approximately 700 mg.

When these capsules were administered to patients, no unpleasant taste was reported after the patients had bitten the capsules.

As a comparison, oral-release capsules (B) closely corresponding to the prior art capsules were prepared, using the same kind of capsule bodies as for the comparison capsules according to the invention.

These capsule bodies were again each filled with approximately 500 mg of solution. The solution contained 10 mg nifedipine, dissolved in a mixture of about 35 mg glycerol, about 409 mg PEG 400, about 44 mg water and about 2 mg peppermint oil and saccharin sodium as taste-improving substances.

The overall weight of these oral-release capsules was thus also approximately 700 mg.

Both kinds of capsules, those according to the invention and those corresponding to prior art, were used in a clinical cross-over study.

For this study, 5 patients were chosen, the personal data of which are given in table I.

TABLE I

Patient	Height (cm)	Weight (kg)	Age (a)	Sex	Appln Sequence	Smoker
1 KLH	177	72	39	m	B/A	+
2 KUJ	177	70	21	m	A/B	+
3 LOG	176	60	31	m	B/A	+
4 NAG	175	76	29	m	B/A	-
5 ROL	178	70	25	m	A/B	+
Mean:	176.6	69.6	29.0			
SDev:	1.1	5.9	6.8			
CV:	.01	.08	.23			

The capsules were administered orally; the mouth cavities of all patients were normal. In Table I and the following tables, A represents the capsules according to the invention, while B represents the prior art capsules.

Table II contains data for nifedipine concentration in serum (ng/ml) after administration of capsules A.

TABLE II

	Patient							
Time	1	2	3	4	5	Mean	SDev	CV
00:00	0	0	0	0	0	0	0	0.000
00:04	0	0	0	0	0	0	0	0.000
00:08	6	9	7	26	12	12	8	0.671
00:12	19	39	11	53	8	26	19	0.733
00:16	35	118	33	117	19	64	49	0.757
00:20	55	121	61	124	31	78	42	0.532
00:30	90	102	47	130	86	91	30	0.329
00:45	78	85	44	105	116	86	28	0.326
01:00	60	69	40	68	132	74	35	0.467
01:30	49	66	28	53	78	55	19	0.338
02:00	25	41	24	35	37	32	8	0.236
03:00	23	27	13	20	37	24	9	0.377
05:00	12	10	5	7	23	12	7	0.603
08:00	8	2	0	4	10	5	4	0.879
10:00	0	0	0	0	6	1	3	2.236

Table III shows the comparison data of nifedipine concentration in serum (ng/ml) after administration of capsules B.

TABLE III

	Patient							
Time	1	2	3	4	5	Mean	SDev	CV
00:00	0	0	0	0	0	0	0	0.000
00:04	0	0	0	0	0	0	0	0.000
00:08	2	0	5	7	21	7	8	1.155
00:12	6	7	6	14	127	32	53	1.675
00:16	8	16	10	22	160	43	66	1.516
00:20	11	24	15	31	167	50	66	1.330
00:30	26	43	24	45	146	57	51	0.890
00:45	22	32	38	49	121	52	40	0.760
01:00	24	33	65	46	111	56	35	0.623
01:30	33	30	39	29	83	43	23	0.529
02:00	40	64	25	25	53	41	17	0.412
03:00	21	30	18	44	36	30	11	0.364
05:00	11	13	5	11	17	11	4	0.387
08:00	5	7	0	9	9	6	4	0.620
10:00	0	0	0	3	5	2	2	1.421

In Figure 1 the average values of nifedipine serum concentration data for capsules A and B are compared for all patients.

Table IV lists the areas under the curves (ng/mlxh) for AUC_{0-10}.

TABLE IV

Patient	A	B
1	198.7	139.8
2	228.4	190.2
3	109.8	119.1
4	216.5	199.9
5	314.3	346.4
Mean	213.5	199.1
SDev	73.1	89.0
CV	0.342	0.447

Table V lists the areas under the curves (ng/mlxh) for $AUC_{0-\infty}$.

TABLE V

Patient	A	B
1	225.3	153.0
2	230.5	207.3
3	112.0	120.8
4	223.5	213.2
5	338.9	366.0
Mean	226.1	212.1
SDev	80.3	94.2
CV	0.355	0.444

Table VI lists the concentration maxima (ng/ml).

TABLE VI

Patient	A	B
1	89.8	40.4
2	121.0	63.5
3	60.9	64.7
4	130.0	49.2
5	132.0	167.0
Mean	106.7	77.0
SDev	30.7	51.3
CV	0.288	0.667

Table VII lists the time durations (h) for attaining the maxima of table VI.

TABLE VII

Patient	A	B
1	0.50	2.00
2	0.33	2.00
3	0.33	1.00
4	0.50	0.75
5	1.00	0.33
Mean	0.53	1.22
SDev	0.27	0.75
CV	0.513	0.619

Table VIII lists the time durations (h) for attaining a serum concentration of 15 ng/ml (t_{MEC}).

TABLE VIII

Patient	A	B
1	0.179	0.378
2	0.147	0.258
3	0.212	0.330
4	0.105	0.206
5	0.241	0.115
Mean	0.177	0.258
SDev	0.053	0.103
CV	0.302	0.401

Table IX lists the elimination constants (h^{-1}).

TABLE IX

Patient	A	B
1	0.220	0.278
2	0.506	0.287
3	0.517	0.543
4	0.337	0.240
5	0.258	0.251
Mean	0.367	0.320
SDev	0.138	0.126
CV	0.376	0.394

The average terminal half-time for capsules A (invention) results as 1.89 h, while the average terminal half-time for capsules B (prior art) is 2.17 h.

As the data show, the required bioavailability levels are reached significantly faster upon administration of capsules A according to the invention.

Since in the practical use of nifedipine preparations, it is of the utmost importance to attain the required degree of bioavailability as fast as possible, the advantages provided by the invention are clear.

Claims

1. An instant oral-release capsule containing an aqueous or aqueous alcoholic solution of nifedipine, a polyalkylene glycol and a polyoxyethylene ester component, the amount of the polyoxyethylene ester component in the solution being sufficient to prevent precipitation of nifedipine in the mouth of a patient after release of the solution from the capsule.

2. Capsule according to claim 1, the polyoxyethylene ester component being substantially of neutral taste.

3. Capsule according to claim 1 or 2, the polyoxyethylene ester component comprising an ethoxylated glyceride, especially a mono- or triglyceride, an ethoxylated fatty acid ester, or an ethoxylated castor oil derivative, or a mixture of two or more of said substances.

4. Capsule according to claim 3, the polyoxyethylene ester component comprising ethoxylated hydrogenated castor oil, especially Cremophor RH40.

5. Capsule according to any one of claims 1 through 4, the solution containing between about 3 and 33 weight percent, especially about 7 to 15 weight percent of the polyoxyethylene ester component.

6. Capsule according to any one of claims 1 through 5, the polyalkylene glycol being polyethylene glycol.

7. Capsule according to claim 6, the polyethylene glycol having an average molecular weight smaller than 2000.

8. Capsule according to claim 7, the polyethylene glycol having an average molecular weight of about 400.

9. Capsule according to any one of claims 1 through 8, the amount of the polyalkylene glycol in the solution being between about 50 and 90 weight percent, especially about 70 to 85 weight percent of the solution.

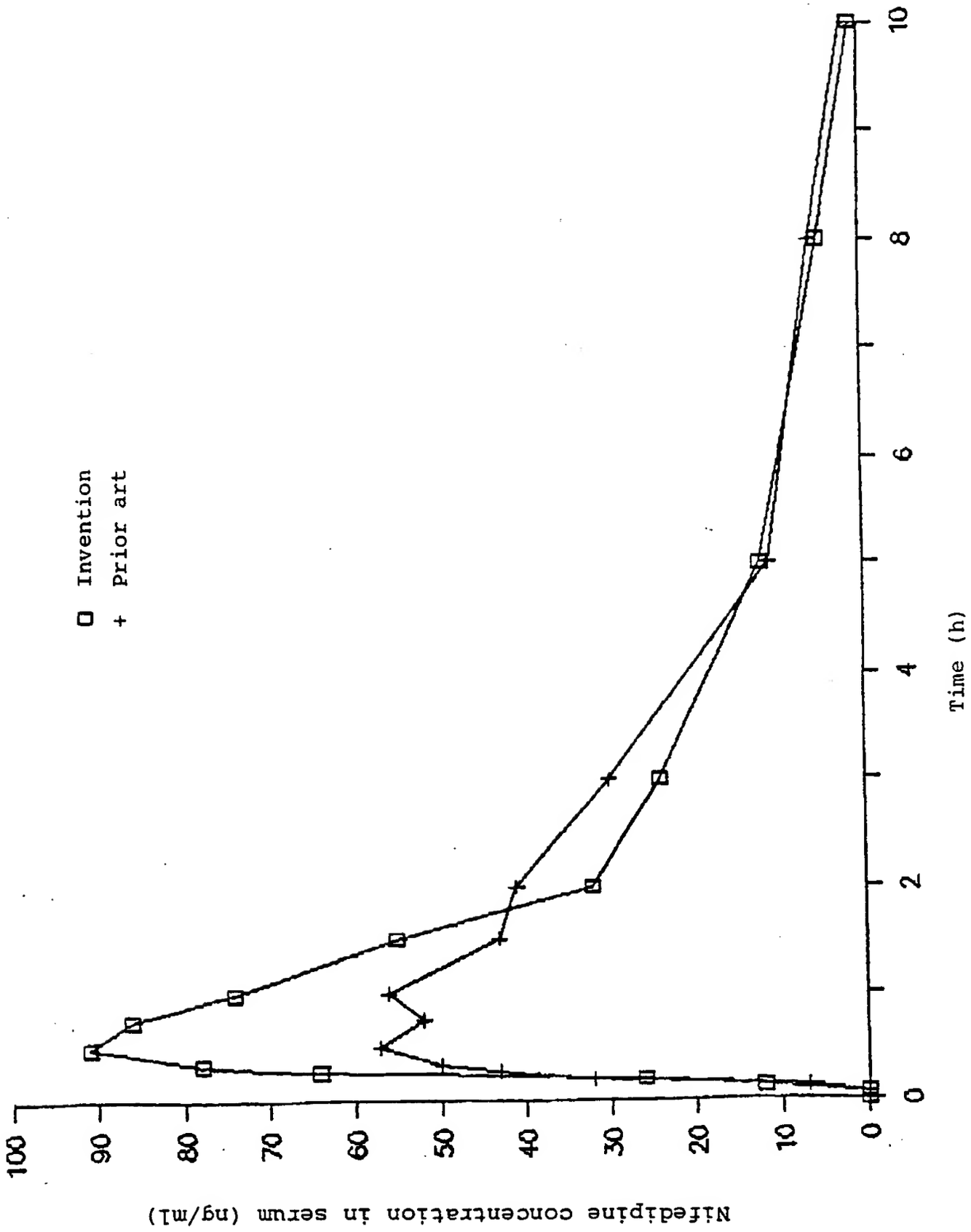
10. Capsule according to any one of claims 1 through 9, the solution further containing a second glycol component.

11. Capsule according to claim 10, the second glycol component being glycerol.

12. Capsule according to claim 10 or 11, the amount of the second glycol component in the solution being between about 2 and 15 weight percent, especially about 5 to 10 weight percent of the solution.

13. Capsule according to any one of claims 1 through 12, the capsule body being formed of soft gelatin containing light-protective pigment.

14. Capsule according to any one of claims 1 through 13, the capsule containing about 500 mg of solution, the solution containing about 10 mg nifedipine, about 403 mg polyethylene glycol with an average molecular weight of about 400, about 35 mg glycerol, about 41 mg ethoxylated hydrogenated castor oil Cremophor RH40, about 9.5 mg water and about 1.5 mg taste-improving substances.


Nifedipine concentration in serum (ng/ml)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
Time (h)
Invention
Prior art

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 11 8596

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X Y	EP-A-0 117 888 (BAYER AG) * Page 7, lines 9-26; page 8, lines 7-16; example 8; claims *	1-3,5-10,12 1,4,13,14	A 61 K 31/44 A 61 K 47/00 A 61 K 9/66
P,X	EP-A-0 278 168 (HARRIS PHARMACEUTICALS LTD) * Whole document *	1-3,5-10,12	
D,Y	LU-A- 65 929 (BAYER AG) * Claims * & DE-A-2 209 526	1,13	
Y	EP-A-0 249 587 (A.B. HÄSSLE) * Example 5; claims * & AU-B-70043/87 (15-10-1987)	1,4,14	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	26-01-1989	BERTE M.J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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